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# Is Melatonin an Effective Treatment for Sleep Problems in Autism?

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# Is Melatonin An Effective Treatment for Sleep Problems in Autism?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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## Abstract

Objective: The objective of this selective EBM review is to determine whether or not melatonin is an effective treatment for sleep problems in Autism.

Study Design: Review of three English language, randomized controlled blinded trials published within peer-reviewed journals from 2006-2010 evaluating the efficacy of Melatonin as an oral sleep supplement in diagnosed autistic children.

Data Sources: A double blind, randomized, placebo-controlled, crossover trial; a randomized controlled crossover trial; and a randomized controlled trial found using Cochrane, PubMed, and DynaMed.

Outcomes Measured: Total night's sleep duration, number of awakenings, and sleep latency time were all measured using both sleep diaries, completed by the parents or caregivers, as well as Actiwatch, a device worn to measure the activity of a participant. Common side effects of Melatonin were measured using a Side Effects Questionnaire (SEQ).

Results: Wirojanan *et al.* 2008 reported night sleep duration was longer on Melatonin than placebo by 21 minutes (p=0.02). Wright *et al.* 2010 reported a significant difference between Melatonin and placebo in total sleep by an average of 52.3 minutes (p=0.002). Garstang *et al.* 2006 reported an increase from 8.05h to 9.84h total sleep duration.

Wirojanan *et al.* 2008 and Wright *et al.* 2010 reported no significant difference in number of night awakenings. Garstang *et al.* 2006 reported a difference between 0.35 baseline to 0.08 with Melatonin.

Wirojanan *et al.* 2008 reported a mean sleep-onset latency shorter by 28 minutes (p=0.0001). Wright *et al.* 2010 reported an improvement of sleep latency by an average of 47 min (p=0.004). Garstang *et al.* 2006 reported a difference in sleep latency from 2.6h baseline to 1.06h with use of Melatonin. Wright *et al.* 2010 reported no significant side effects in the SEQ.

Conclusion: The results of the three studies presented evidence that the use of Melatonin to improve sleep problems in children with Autism is a safe and effective treatment option. While there is no significant improvement in the number of times a child awakens during the night, there is statistical significance to show using Melatonin improves sleep latency and total night's sleep.



Key Words: Autism and Melatonin

## Introduction

The National Institute of Neurological Disorders and Stroke defines autism by a range of complex neurodevelopment disorders, characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior[1]. There are different types of autism that all fall within what clinicians call a spectrum, thus the term Autism Spectrum Disorder (ASD). The spectrum ranges from classical ASD, the most severe form, to Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS).

The incidence of autism has been increasing rapidly over the past decade. The CDC's Autism and Developmental Disabilities Monitoring Network (ADDM) estimates about 1 in 88 children have been identified with ASD[2]. While there is no difference in race, ethnic, and socioeconomic groups there is a predilection for sex. ASD is five times more common in males (1 in 54) than in females (1 in 252)[2]. The cause of the rise in numbers is currently unknown and, because the cause of autism has yet to be identified, these numbers will continue to increase. This problem is not only a cause for concern within the general public but also within the medical profession because there are many medical needs for a child with autism.

Sleep disturbances are reported in up to 89% of children with autism[3]. Some of the most common sleep dyssomnias reported in children with autism are difficulties falling asleep, recurrent night awakenings, and total length of time asleep. The occurrence of sleep disturbances put children with autism at greater risk for more complex complications like further developmental delays, behavioral difficulties, and psychological concerns[3]. These sleep disturbances can cause issues not only for the child but the caretaker as well. As physician assistants it is our duty to not only give guidance to parents with autistic children but also to better the lives of the children themselves.

Melatonin is an inexpensive and readily available, over the counter solution for not only autistic children with sleep disturbances but also for the general public with sleep difficulties. A bottle of 100 3mg tablets costs $5.99 in a drug store like GNC or CVS[4]. This cost is far less than any prescribed sleep aid such as Ambien CR, Lunesta, and Sonata that costs an average of $56, $56, and $38 respectively for only seven doses[5].

Autism is a multisystem condition that has to be handled by a wide range of physicians. While a pediatrician can handle the child's overall health and any acute problems that arise, psychologists and speech therapists should handle issues such as cognitive delay and speech. Physical therapists can be referred to for musculature and motor function complications. By improving the child's sleep you therefore improve their growth, behavior issues, and psychological problems. It is therefore assumed that with better general overall health autistic patients would have less frequent office visits.

There are many different hypotheses about why children with ASD have sleep disturbances. One of the most recent theories involves the N-Acetylserotonin O-methyltransferase (ASMT) gene that is responsible for encoding the last enzyme of melatonin synthesis. In children with ASD, this gene was shown to be significantly less active, thus indicating lower levels of melatonin[6].

Current treatment for children that have ASD with associated sleep disturbances includes antiepileptic therapies such as carbamazepine, gabapentin, topiramate, and valproic acid; psychological therapies including behavioral management and one-on-one therapy sessions; and antidepressants like mirtazapine and trazodone[7].

Melatonin has been used to treat insomnia associated with shift work, jet lag, and delayed sleep for decades[3]. It is thought that because there has been evidence that suggests children with

ASD have a lower blood level of melatonin at night, synthetically substituting the melatonin will improve sleep.

**Objective**

The objective of this selective EBM review is to determine whether or not melatonin is an effective treatment for sleep problems in autism.

**Methods**

Patients in this study were between the ages of 2 and 16 years old with a diagnosed autism spectrum disorder that have significant sleep difficulties as reported by either their parents or physicians. One study reviewed is a double blind, randomized, placebo-controlled, crossover trial[3]. Another is a randomized, controlled, crossover trial[6]. Finally, the third study reviewed is a randomized controlled trial[8]. The intervention evaluated throughout the three trials was giving the participant a dose of melatonin between 2 and 10 mg before bedtime. In one of the studies the child was started on 2mg 30-40 minutes prior to bedtime and titrated every three nights by 2 mg to a max of 10 mg until "good sleep was achieved[6]. Another study allowed only 3 mg of medication delivered 30 minutes prior to bedtime over a two-week trial[3]. Finally a study gave participants a 5 mg dose of medication for four weeks[8]. The comparison to the treatment group receiving melatonin was the experimental group who received a visually matched placebo. The outcomes analyzed all qualified as patient oriented evidence that matters (POEMs) and included total night's sleep duration, number of awakenings, and sleep latency time.

The three studies reviewed were all written in English and published in peer-reviewed journals (Journal of Autism Development Disorder, Journal of Clinical Sleep Medicine, and The Authors Journal) in the years of 2006,2008, and 2010. The author using key words autism and melatonin performed a detailed search using research databases such as PubMed, Cochrane, and

DynaMed. Table 1 illustrates the specific inclusion and exclusion criteria for each study. Inclusion criteria included children between the ages of 2 and 16 years old diagnosed with ASD by a pediatrician, psychologist, and WHO research diagnostic criteria without successful behavior management and free of medications. Exclusion criteria included children who had previously used melatonin as well as children currently on any sedative or psychotropic medication. One study allowed children to participate if there was a 4-week medication free period completed prior to the trial[8]. The summary of statistics reported and utilized in the studies were confidence intervals (CI), p-values, relative risk increase (RRI), absolute risk increase (ARI), and number needed to harm (NNH).

**Table 1: Demographics & Characteristics of included studies**

| Study | Type | # Pts | Age (yrs) | Inclusion Criteria | Exclusion Criteria | W/D | Interventions |
|---|---|---|---|---|---|---|---|
| Garstang (2006) | Randomized placebo-controlled double blind trial | 11 | 4-16 | - Diagnosed with ASD by a pediatrician or psychologist<br>- Children with learning disabilities, ADHD, and dyspraxia | -Children that had used melatonin previously<br>-Children who had been using other sedative medication not allowed trial entry until they had completed 4 weeks of medication | 4 | Regime of 5mg of melatonin |
| Wright (2010) | Double blind randomized controlled crossover trial | 20 | 3-16 | -Children with ASD who had been referred because of serious sleep problems<br>-ASD diagnosed based on WHO research diagnostic criteria<br>-Non successful | -Children previously or currently on melatonin<br>-On psychotropic medication<br>-Those suffering from related disorders like Fragile X or Rett's | 3 | Started on 2mg melatonin 30-40 minutes before bedtime and increased 2mg every three nights to max dose of 10mg |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | behavior management | | | |
| Wirojanan (2008) | Randomized double blind, placebo-controlled, crossover trial | 18 | 2-15.3 | -ASD was diagnosed by a team of developmental pediatricians and psychologists<br>-Free from medications | None | 6 | Regimen of melatonin 3mg, 30 minutes before bedtime. |

**Outcomes Measured**

The outcomes measured in the reviewed studies are all Patient Oriented Evidence that Matters (POEMs). Wirojanan *et al*[3] measured participants after a 1 week baseline period, children were then instructed to take a 2 week medication consisting of either placebo or melatonin 30 minutes prior to bedtime. Total night sleep duration, sleep-onset latency (the time from bedtime to sleep onset time), and number of night awakenings were recorded using a sleep diary, completed by the parent or guardian, and Actiwatch[3]. Actiwatch is a wrist-worn device that measures the activity counts each minute. A count of 100 or above for 2 consecutive minutes was considered the beginning of an awakening[3]. Differences between the melatonin group and placebo group were compared and analyzed via p-values. Wright *et al*[6] measured a baseline for two groups for 1 month. Sleep diaries were kept by the parent or guardian and collected by the researcher every month for 9 months. These sleep diaries recorded sleep latency (time from starting bedtime routine to sleep), total sleep time, and number of awakenings. These values were again analyzed via p-values. A Side Effects Questionnaire (SEQ) was also kept by the parents recording all literature and manufacturer reported side effects for melatonin, theoretical side effects, common generic side effects and any other noted changes in health and wellbeing[6]. These results were analyzed and reported using p-value. Garstang *et al*[8] measured a baseline

assessment for 1 week before the medication was distributed. Once the medication was distributed a 4 week monitoring period went on where the parents used a sleep chart to record the total sleep time, sleep latency, and number of awakenings. This data was then analyzed using 95% confidence intervals for the baseline period, placebo period, and melatonin period.

**Results**

In the study performed by Wirojanan et al,[3] 18 patients (16 boys, 2 girls) ages 2 to 15.3 years old were recruited through the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D) Institute clinic at the University of California, Davis. The participants were given a number based on the order they were enrolled in the study. The document identifying the patient to their number was locked in the investigator's file until the study concluded[3]. Patients conducted a 1-week baseline period and then randomized into treatment and placebo groups. The participants were told to administer 3mg oral medication 30 minutes prior to bedtime[3]. For all three studies, statistical analysis was done on the intent to treat (ITT) population. This study only included continuous data that could not be converted into dichotomous data.

Six participants were not included in the final results of the study. Three of the six were excluded because their caregiver failed to complete the sleep diaries. Another was excluded because their Actiwatch was not worn during the treatment block. One of the subjects was excluded because their Actiwatch was not worn during the intervention block. Finally, one other was excluded because the family did not follow the studies protocol[3].

The total night's sleep, sleep latency time, and number of night awakenings were recorded using both actigraph and a daily sleep diary. Actiwatch data consisted of activity counts for each 1-minute epoch[3]. This data was extracted from the watch and analyzed with ActiWare software. The criteria for a child to be considered awake was an activity count of 100 or above

for two consecutive minutes[3]. All participants' data was used in a complete case analysis (CC), in which only cases that completed all observations were included[3]. Parametric *t*-test was also used to compare the averages of all participants[3]. P-value was recorded and determined to be significant for both night sleep duration and sleep-latency time (see table 2)[3]. While number of night awakenings did not demonstrate a significant p-value table 3 demonstrates there was a decrease while on melatonin.

**Table 2:** Nonparametric Analysis of the Sleep Variables for the CC Data Set

| Sleep variables | Data set | p Value |
|---|---|---|
| Night sleep duration | CC | 0.0019 |
| Sleep-latency time | CC | 0.0001 |
| Number of night awakenings | CC | 0.93 |

**Table 3:** Comparison of Sleep Variables During Placebo and Melatonin

| Variables | Placebo | Melatonin | p Value |
|---|---|---|---|
| **Total night sleep duration, h:min** | 7:54 (1:07) | 8:15 (1:15) | 0.057 |
| **Sleep-latency time, min:s** | 53:35 (60:33) | 25:30 (16:53) | 0.10 |
| **Awakenings, no./night** | 2.07 (1.5) | 1.99 (1.2) | 0.73 |

In the study performed by Wright et al[6], 20 children (16 male, 4 female) ranging from ages 4 to 16 years old were selected to participate in the study[6]. They were selected after being referred for serious sleep problems by their pediatrician or specialist CAMHS (child and adolescent mental health services). Children excluded were those previously or currently on melatonin, those currently on psychotropic medication, and those suffering from related developmental or neurological disorder, such as Fragile X or Rett syndrome[6]. Children also had to have had previous behavior management that had failed to be included.

Seventeen patients completed the study and were included in the final data[6]. One participant dropped out because it was too difficult to give medication, one because the guardian

did not complete the diary, one because of significant benefits, and one because of apparent ineffectiveness of the medication[6]. These seventeen were randomized into treatment and placebo groups. A sleep diary was kept in order to record data for total sleep, sleep latency, and number of awakenings[6]. A side effects questionnaire (SEQ) to measure all literature and manufacturer reported side effects for melatonin, theoretical side effects, common generic side effects and any other noted changes in health or wellbeing was taken at the start of the study, end of the study, and after every 3 month period[6].

After randomizing the 2 groups, everyone was monitored for 1 month to get a baseline. Then patients were placed on either placebo or melatonin for 3 months. Everyone started on 2 mg 30-40 minutes before bedtime[6]. The parents increased the dose every three nights by 2mg maxing out at 10 mg[6]. If guardian noticed "good sleep" the child was stabilized at that current dosage[6]. For data in the SEQ, baseline scores were compared using Mann-Whitney *U*- Test[6]. For melatonin and placebo score comparison a Wilcoxon Signed Ranks Test was used[6]. All analyses were performed on SPSS and a p-value of $<0.05$ was considered to indicate statistical significance[6]. There was statistical significance in sleep latency and total sleep (table 4). However, there was no significance in number of night awakenings. Also, there was no significance reported for the SEQ. Stating all reported side effects had a p-value of greater than 0.05[6]. Specifically daytime drowsiness had a CER of 68.8% from the placebo and EER of 35.3% from the melatonin. The RRI was determined to be -48.7%. The ARI was calculated at -33.5% and the NNH were determined to be -2.9 (or 3 patients) see table 5.

**Table 4:** Mean scores on sleep diary, general health questionnaire, and sleep difficulties questionnaire for baseline, melatonin and placebo arms of the trial

| Sleep diary | Baseline | Melatonin | Placebo | Mean difference | Test statistic |
|---|---|---|---|---|---|
| **Sleep latency (min)** | 135.0 (63.0) | 82.84 (50.61) | 124.79 | 46.7 (55) | $t(15)=3.394$, $p=0.004$ |

| | | | | | |
|---|---|---|---|---|---|
| **No. of awakenings** | 0.5 (0.5) | 0.43 (0.64) | 0.58 (0.74) | 0.1 (0.4) | $t(15)=1.313$, $p=0.209$ |
| **Total sleep [min]** | 499.9 (66.4) | 556.11 (53.59) | 507.66 (70.67) | 52.3 (55.1) | $t=3.75$, $p=0.002$ |

**Table 5:** SEQ Calculations

| YOUR CALCULATIONS for Harm – using dichotomous data **Daytime Drowsiness** | | **Relative risk increase (RRI)** | **Absolute risk increase (ARI)** | **Number needed to harm (NNH)** |
|---|---|---|---|---|
| CER<br><br>Placebo | EER<br><br>Melatonin | $\frac{\text{EER- CER}}{\text{CER}}$<br>$\frac{35.3 - 68.8}{68.8}$ | EER – CER<br><br>35.3 – 68.8 | 1/ARI<br><br>1/-33.5 |
| 68.8% | 35.3% | - 48.7% | - 33.5% | - 3 (3 patients) |

In the study performed by Garstang et al[8], 11 children (7 male, 4 female) ranging from ages 4 to 16 years old were selected to participate by recruitment from community pediatricians, special schools, local autism-support service and local parent-support groups[8]. Children who had used melatonin previously were excluded[8]. While children who had been using other sedative medication had to complete a 4-week medication free trial before allowed entry.

Seven children completed the study. The trial had to be suspended because of the placebo pill being empty. This suspension forced two girls to drop out[8]. One boy dropped out because of a housing relocation and one girl became involved in a child protection enquiry[8].

Children were randomized into either the treatment or placebo group at the beginning of the study. A sleep diary taken by the guardian was used to measure total sleep, wakings per night and sleep latency. Their guardians were told to keep a 1-week sleep diary prior to the study beginning in order to establish a baseline[8]. The participants were then given 5mg of either melatonin or a look-a-like placebo and told to take orally before bedtime[8]. The guardians were advised to keep a sleep diary recording total sleep time, sleep latency and night awakenings for 4 weeks. A 1-week washout was performed and then another 4-week trial was started[8]. The mean

and 95% Confidence interval (CI) were calculated and reported (see table 6). The study reported that all children completing the study remained on melatonin and that 75% of patients that dropped out were eventually prescribed melatonin[8].

**Table 6**: Mean and 95% confidence intervals (CI) of treatment on sleep patterns

| | Sleep latency (h) | | Wakings per night | | Total sleep (h) | |
|---|---|---|---|---|---|---|
| | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI |
| **Baseline** | 2.60 | 2.28-2.93 | 0.35 | 0.18-0.53 | 8.05 | 7.65-8.44 |
| **Placebo** | 1.91 | 1.78-2.03 | 0.26 | 0.20-0.34 | 8.75 | 8.56-8.98 |
| **Melatonin** | 1.06 | 0.98-1.13 | 0.08 | 0.04-0.12 | 9.84 | 9.68-9.99 |

## Discussion

This systematic review investigated three studies to determine whether or not the use of melatonin in children with ASD was a viable option to treat and improve sleep patterns. All three studies demonstrated that the use of melatonin significantly improved total night sleep and sleep latency times when compared to the placebo.

While all three studies used different dosages of melatonin it is undetermined as to whether or not melatonin is a better treatment option when compared to other current pharmacological treatments like antiepileptic therapies or antidepressants. Wirojanan *et al.* conclude that the use of melatonin in combination with behavior therapies and proper sleep hygiene practices should be used for best effective results[3].

Among the studies included in this selective review, there were several limitations expressed by each study. In both Wright et al. and Wirojanan et al. studies, the suggestion that bioavailability and metabolism may play a role into the effectiveness of being treated with a set dosage of melatonin was discussed. Wirojanan et al stating, “some participants may have needed higher dose for obtaining a significant response, whereas other might have benefited from lower dose.”[3] While Wright et al. used a dosing range of 2mg to 10 mg and stating, “some children

may require larger doses than those being suggested in literature, and that there may be considerable variability in dose needed."[6]. Additionally, both Wright et al. and Garstang et al. reported small sample sizes and difficulty with recruiting. Garstang et al. suggested that in future studies a multi-centre approach should be used because many of the participants were excluded because melatonin was already being used in their child with ASD.

**Conclusion**

Based on the information provided in these three studies, it has been concluded that Melatonin is an effective treatment for children that struggle with sleep problems compared to placebo at doses of 2mg to 10 mg. However, there are several issues with these studies that would require further examination. One main concern is the amount of children enrolled in all three studies. All three consisted of small numbers of participants, which can skew what a full spectrum view of the average population with ASD would look like. Another issue is bioavailability. One study allowed participants a dose range of 2mg to 10 mg while the other two studies only allowed a 3mg dose and 5mg dose. Due to the different severity types of ASD it is not known whether children with a more severe form of ASD require a larger dose of melatonin versus the children with a less severe form of ASD.

Future studies in this area of concern should be conducted to discuss the exact dosage of melatonin needed to increase outcomes of better sleep. These studies would have to be longer in length due to different groups testing different dosages of melatonin. Also instead of a wristband to measure sleep activity a camera could be installed in the child's room to visually record the number of night awakenings. Neurologists and Pulmonologists should also be consulted to further classify when a participant is termed "awake" versus other psychological abnormalities.

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